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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/025,514	12/18/2001	Philip J. Barr	368292000200	6421

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EXAMINER
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WALICKA, MALGORZATA A

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 03/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/025,514

Applicant(s)

BARR ET AL.

Examiner

Malgorzata A. Walicka

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 23 November 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 2, 4, 8, 16-17, 26-42 and 46-49 are pending. is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 4, 16, 17, 36-39 and 41 is/are allowed.
- 6) ☐ Claim(s) 2, 8, 42 and 49 is/are rejected.
- 7) ☒ Claim(s) 47 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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Amendment and Response to Office Action filed Nov. 23, 2005 is acknowledged.

Claims 1 and 11 were previously cancelled. Claims 3, 5, 7, 9-10, 12-15, 18-25 and 43-45 are currently canceled. Claims 2, 4, 8, and 42 have been currently amended. New claims 46-49 have been added. Claims 2, 4, 8, 16-17, 26-42 and 46-49 are pending. Claims 2, 4, 8, 16, 17, 36, 37 and 42 and 46-49 directed to the elected invention are the subject of this Office Action. In addition, 38-39 and 41 directed to a method of use of allowable product are under examination. Claims 26-35 and 40 will be consider for rejoinder at such time as allowable composition claims are identified.

### **Detailed Office Action**

#### **1. Objections withdrawal and claim rejoinder**

Claims 4, 16, 17, 36, 37, 41 were objected to in the Office Action of August 24, 2005 (previous action) as depending on rejected claim 2 but would be allowable if rewritten in an independent form. After the current amendment the claims are no longer dependent on rejected claim 2 and thus the objection is withdrawn.

Claim 4 is directed to an allowable product. Pursuant to the procedures set forth in MPEP § 821.04(B), claims 38-39 and 40, directed to the process of making or using an allowable product, previously withdrawn from consideration as a result of a restriction requirement, are hereby rejoined and fully examined for patentability under 37 CFR 1.104. Claims 26-35, directed to the invention(s) of use of the product of claim 2 or 4 require all the limitations of an allowable product claim, and claims 26-36 are NOT been rejoined.

## **2. Rejections**

### **2.1. 35 U.S.C. 112, second paragraph**

Claims 42-45 were rejected under 35 U.S.C. 112, second paragraph, in previous action. Rejection of claim 42 is withdrawn, because the claim has been amended. Rejection of claims 43-45 is moot because the claims have been canceled.

### **2.2. 35 U.S.C. 112, first paragraph**

#### Lack of written description

Claims 42-45 were rejected in the previous action are rejected under 35 U.S.C. 112, first paragraph in the previous action as failing to comply with the written description requirement. The rejection of claim 42 is withdrawn because the claim has been amended. Rejection of claims 43-45 is moot because the claims have been canceled.

### **2.3. Rejection under 35 U.S.C 103**

Claims 2, 8, claim 42 and new dependent claim 49 are rejected 35 U.S.C. 103(a) as being unpatentable over Urwin P. et al, (*Enhanced transgenic plant resistance to nematodes by dual proteinase inhibitor constructs*, *Planta*, 1998, 204, 472-479, attached) and WO 92/10575 document published 1992 (attached) in view of the article by Bingle L. et al., (*Secretory leucoprotease inhibitor: partnering alpha 1-proteinase inhibitor to combat pulmonary inflammation*, *Thorax*, Dec. 1996, vol. 51/12, pages 1273-1274; a copy enclosed to the Office Action of July 22, 2004).

The reason for the rejection were explained in previous action. The fact that the claims are now directed to functionally active portions of both serpins does not change the way of examiner's argumentation. The claims are directed to a fusion protein comprising a functionally active portion of alpha 1-antitrypsin and a functionally active portion of secretory leukocyte protease inhibitor, wherein said fusion protein has alpha 1-antitrypsin activity and secretory leukocyte protease inhibitor activity or to a fusion protein comprising elastase inhibitory domain of AAT and trypase inhibitory domain of SLPI.

Urwin et al. teach a dual protease inhibitor consisting of full-length cystein (CPT1) and serine protease (Oc-IAD86) inhibitors from intestines of *Nemathode*. The fusion inhibitor, called Oc-IAD86/GO/CpT1 was expressed in plant and shown to *in vivo* protected this organism against *Nemathode* infections. The efficiency of protection was higher than in case when both inhibitors were acting separately. See results in Table 2 and 3 and the comment on page 476 right column above the paragraph **Discussion**. In the comment the authors state that the fusion protein had an additive effect of both protein inhibitors. Thus, Urwin et al. teach that the whole molecules of protease inhibitors can be combined in a fusion protein retaining their activities.

WO documents teaches bifunctional inhibitors of thrombin and platelet activation (disintegrins), wherein said bifunctional inhibitors comprise inhibitory domains of both inhibitors from different sources. The fusion protein is constructed by linking combining N-terminus of one peptide to C terminus of the second peptides or *vice versa* (page 15, line 22). The fusion proteins are set forth by SEQ ID NO: 2-9; see page 22 and further.

The document teaches also production of fusion proteins in host cells, purification of the fusion proteins and their use for treating thrombotic disease. The examples of the WO document disclose many activities of the fusion proteins related to thrombosis.

Urwin et al. and WO documents teach that protease inhibitors used as a whole or as as their active fragments may be combined in fusion proteins that retain their inhibitory functions. Neither Urwin nor WO document teach the fusion protein consisting of alpha 1-antitrypsin and secretory leukocyte inhibitor or of their active parts.

Bingle et al. teaches, "SLPI is a significant component of the anti-NE [neutrophil elastase] shield in the lung, which has different reactivity from, and is therefore complementary to, the anti-NE action of  $\alpha_1$ -proteinase inhibitor"; see the Abstract. Furthermore, Bingle et al. strongly suggest that secretory leukocyte protease inhibitor and alpha 1-protease inhibitor, i.e. alpha 1-antitrypsin, are the most effective for treatment of inflammatory lung disorders such as emphysema, bronchiectasis, pulmonary fibrosis, acute lung injury and bronchopulmonary dysplasia **when used in combination**; see page 1274, the text bridging the left and right column. The "combination" or "partnering", announced in the title, means to associate as a partner, which in the disputable case of use of two proteins includes also their fusion.

It would have been obvious to one having ordinary skill in the art at the time of invention to have a bifunctional fusion protein consisting of full-length protease inhibitors as taught by Urwin et al. or WO fusion protein consisting of the active parts of protease inhibitors and modify them so that they comprised alpha 1-antitrypsin and SLPI or their functionally active parts. The motivation to combine alpha 1-antitrypsin and human

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secretory leucocyte inhibitor in one fusion protein was provided by Bingle et al., because they teach that combination of both activities as partners is of high therapeutic importance, and a fusion provide the closest partnership. The therapeutic importance of such composition is the greater that the SLPI has also been shown to possess anti-HIV activity at physiological concentrations. Therefore, combining both serpins in one protein would provide a therapeutic fighting a large number of lung disorders including those related to HIV. The expectation of success was very high because Urwin and WO document teach that fusion proteins comprising the full-length or functionally active parts of protease inhibitors remain activities of their components.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Traversing this rejection Applicants submit,

“[t]he prior art references alone or in combination fail to teach each element of the claims. Specifically there is no teaching in the WO reference, Urwin or Bingle either alone or in combination of a fusion protein of functionally active portion of alpha 1-antitrypsin fused with functionally active portion of SLPI.”

Applicants' argument has been fully considered but is found not persuasive.

The rejection is made under 35 USC section 103, and not under 35 USC section 102. The prior art reference as applied in rejection under 35 USC 103 make the invention obvious for the person having ordinary skill in the art, and does not teach every limitation of the claims.

In summary, claims 2, 8, claim 42, and new dependent claim 49, are rejected.

### 3. Conclusion

Claims 4, 16, 17, 36, 37, ~~41~~, and 48 are allowed for reasons presented in previous Office Actions. Claims 38-39 and 41 are also allowed as directed to the allowable product whose method of use for inhibition of proteases and treatment recited human diseases are taught by the disclosure.

Claim 47 is objected to as being dependent upon a rejected base claim 2 or 42, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is




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(571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Malgorzata A. Walicka, Ph.D.  
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